Leukemia Research Reports 1 (2012) 7–8

Contents lists available at SciVerse ScienceDirect

Leukemia Research Reports

journal homepage: www.elsevier.com/locate/lrr

Case Report

New diagnosis of multiple myeloma in a patient with mantle cell lymphoma: Shared genetic factors or simple coincidence?

Mutende J. Sikuyayenga *, Craig B. Reeder, Joseph R. Mikhael

Division of Hematology-Oncology, Mayo Clinic, Scottsdale, AZ, United States

ARTICLE INFO

Article history:
Received 27 July 2012
Received in revised form
14 September 2012
Accepted 18 September 2012
Available online 10 November 2012

Keywords:
Multiple myeloma
Mantle cell lymphoma
t(11;14)(q13;q32)

ABSTRACT

Multiple Myeloma and Mantle Cell Lymphoma are well defined hematological malignancies. Understanding of their pathogeneses has led to new therapies and increased survival. We report on a 64-yr-old female who was diagnosed with mantle cell lymphoma in 2003, then multiple myeloma in 2010. We identified only few other cases of concomitant MM and MCL. We also explored the importance of t(11;14)(q13;q32). The development of these two disorders in the same patient may simply be due to chance; however, it may also represent a common genetic hit affecting the B-cell population leading to development of two different malignancies.

Multiple myeloma and mantle cell lymphoma are well defined B-cell malignancies with significant disease burden worldwide. Understanding of the pathogenesis of both entities has improved over the years, leading to new therapies and improved survival rates.[1,2] The hallmark of MCL is t(11;14)(q13;q32); this genetic alteration leads to overexpression of cyclin D1, an important regulator of the cell cycle.[3] While the same translocation and overexpression of cyclin D1 has been recognized in a subset of patients with MM, its role in the pathogenesis of myeloma is still undetermined.[4] The occurrence of MCL and MM in the same patient is very rare. To our knowledge, there are only limited case reports of MCL and MM affecting the same patient.[5–9] Here we report a case of MM which arose in a patient previously diagnosed and successfully treated for MCL. We also review literature to explore the relationship, if any, between these two entities to understand how genetic factors might contribute to their development in a single individual.

A 64 yr-old female with no significant past medical history developed lymphadenopathy and splenomegaly in the 1970s. By patient report, all pathology studies obtained following splenectomy were negative for malignancy. In 2003 the patient presented again with generalized lymphadenopathy. A diagnosis of MCL was made; the bone marrow was not involved. After six cycles of cladribine and rituximab, the disease went into remission for four years. In 2007, routine follow-up imaging demonstrated recurrence of lymphadenopathy. An axillary lymph node biopsy was again positive for a monoclonal B cell population characteristic of MCL. Flow cytometry confirmed a clone expressing CD5, CD19, CD20, FMC-7 and kappa light chain. FISH confirmed a CCND1/IgH rearrangement in 63% of cells. There was no evidence of a plasma cell component. The patient completed six cycles of bortezomib, pentostatin, and rituximab. She was then placed on maintenance therapy with rituximab every three months until September 2010.

Shortly after her last dose of rituximab she developed generalized body aches, fatigue, headache, dizziness, and epistaxis. Physical examination was unremarkable except for right tonsillar prominence. Extensive laboratory studies revealed normocytic anemia, mild hypercalcemia, elevated total protein, high serum viscosity, and normal renal function. Special protein studies showed a monoclonal IgM kappa protein, an M-spike of 4 gm/dL and IgM of 7060 mg/dl. Plasmapheresis was started for hyperviscosity syndrome. PET/CT scan showed no diffuse lymphadenopathy or bony lesion; there was a 2-cm mass in the right palatine tonsil region with increased FDG uptake. Biopsy was planned, and then canceled given increased risk of bleeding due to high serum viscosity. Bone marrow aspiration and biopsy showed a hypercellular marrow (60%) with 50% clonal plasma cells consistent with multiple myeloma. There was no evidence of mantle cell lymphoma or lymphoplasmacytic lymphoma. Repeat studies by different institutions confirmed kappa light chain positive myeloma with negative immunostaining for CD5, CD19, CD20, and CD56. Cytogenetic studies revealed a 46, XX female karyotype and the presence of t(11;14) by FISH as the only genetic aberration.

Abbreviations: MM, multiple myeloma; MCL, mantle cell lymphoma; FDG, fluorodeoxyglucose; VCD, velcade (bortezomib) cyclophosphamide dexamethasone; VRD, velcade revlimid (lenalidomide) dexamethasone; G-CSF, granulocyte colony-stimulating factor; PBSCT, peripheral blood stem cell transplantation; VDJ, variable, diverse, joining (region); IgH, immunoglobin heavy (chain)

* Corresponding author. Tel.: +1 480 301 9824; fax: +1 480 301 4171.
E-mail address: Sikuyayenga.mutende@mayo.edu (M.J. Sikuyayenga).

2213-0489
http://dx.doi.org/10.1016/j.lrr.2012.09.003

She had a good response to therapy after receiving four cycles of bortezomib, cyclophosphamide, and dexamethasone (VCD) with the M-spike dropping to as low as 1.2, quantitative IgM to 2060 mg/dl, and plasma cells to only 10 % in the bone marrow. She underwent peripheral blood stem cell (PBSC) collection; 6 million CD34+ cells were collected after administration Plerixafor in addition to high dose G-CSF. Additional three cycles of VCD were given, then cyclophosphamide was replaced by lenalidomide due to poor response. After four cycles of VRD the patient underwent successful autologous PBSCT. Both MM and MCL are currently in remission.

In a letter to the editor of *Leukemia Research*, Dasanu reported the case of a 55-yr-old male diagnosed with t(11;14)+ IgG-lambda MM, who presented with enlarged lymph nodes six years later. Biopsy was consistent with CD5-negative MCL.[5] In 1999, Yamaguchi conducted clonal relationship analysis on myeloma and lymphoma cells obtained from a 76-yr-old male diagnosed with CD5-positive MCL and IgG-kappa MM. He concluded that there was no clonal relationship between the two diseases.[6] However, a recent study of seven MCL cases presenting with a plasma cell component demonstrated that in five patients both MCL and plasma cell clones had identical restriction fragments, and thus a common clonal origin.[9]

In addition to the fact that both diseases arise from B cells, these two malignancies also share some other features including the presence of t(11;14) and the overexpression of cyclin D1. It is suggested that overexpression of this important cell cycle regulator is crucial for malignant cell survival in MCL; on the other hand, the importance of t(11;14) in the pathogenesis of MM remains uncertain. Some investigations concluded that cyclin D1 expression was not essential for the pathogenesis of MM. For example, Fiancette et al. showed that deregulation of CCND1 gene and overexpression of cyclin D1 did not result in accelerated tumorigenesis in mice; thus, concluding that cyclin D1 expression may simply represent a "single hit" in B-cell malignancies and may not in itself be adequate for oncogenesis.[10] However, Marsaud and her partners injected cells that had been genetically modified to express cyclin D1 into immunocompromised mice to test the oncogenic property of this factor. The mice developed malignant tumors at the injection site demonstrating that cyclin D1 is indeed oncogenic.[11] In fact, another animal study also illustrated the oncogenic nature of cyclin D1 expression and proposed a possible mechanism through its nuclear-retention.[12] More recently, Tchakarska and colleagues showed that cyclin D1 might also act by inhibition of mitochondrial metabolism which could potentially lead to loss of apoptosis and, therefore, uncontrolled growth.[13] It is important to point out that although the t(11;14)(q13;q32) can be present in both MCL and MM; the genetic background is different. In the first, the translocation results from VDJ recombinations, and in the later, it is the product of errors in somatic hypermutation within the IgH switch regions.[14,15] Unfortunately, molecular studies of the cancer cells for clonal relationship could not be undertaken in our patient because of lack of adequate MCL sample. Sequencing of the IgH regions from the two cell groups would have been very informative. It is however interesting to speculate about a possible composite disease based on multiple facts; the CD19 negativity which is uncommon in pure plasma cell dyscrasias; high M-spike and other features of multiple myeloma, but poor response to bortezomib as sometimes seen in MCL.

The rarity of concomitant diagnosis of MCL and MM makes it difficult to investigate a possible association. Our patient has two kappa-restricted malignancies with a common genetic mutation, which may suggest a true association; however, in the absence of clonality studies, we can only wonder about their clonal origin. While the investigation done by Yamaguchi and his colleagues in the case reported above concluded that there was no clonal relationship; the studies performed by Visco and colleagues showed the same clonal origin in five cases of MCL with plasma cell component. Although the question about the clinical significance of this genetic aberration shared by MM and MCL seems to be settled, its role in tumorigenesis is an ongoing area of investigation. Further studies may lead to better understanding of the pathogenesis of both MM and MCL and potentially reveal new targets for therapy.

References

1. Palumbo A, Kenneth A. Multiple myeloma. *New England Journal of Medicine* 2011;**364**:1046–60.
2. Perez-Galan P, Dreyling M, Wiestner A. Mantle cell lymphoma: biology, pathogenesis, and the molecular basis of treatment in the genomic era. *Blood* 2011;**117**(1):26–38.
3. Fernandez V, Hartmann E, Ott G, Campo E, Rosenwald A. Pathogenesis of mantle-cell lymphoma: all oncogenic roads lead to dysregulation of cell cycle and dna damage response pathways. *Journal of Clinical Oncology* 2005; **23**(26):6364–9.
4. Hoyer J, Hanson C, Fonseca R, Greipp PR, Dewald GW, Kurtin PJ. The (11;14)(q13;q32) translocation in multiple myeloma: a morphologic and immunohistochemical study. *American Journal of Clinical Pathology* 2000; **113**:831–7.
5. Dasanu C, Bauer F. Mantle cell lymphoma arising in a multiple myeloma patient responding to lenalidomide. *Leukemia Research* 2000;**34**:e178–80.
6. Yamaguchi M, Ohno T, Miyata E. Analysis of clonal relationship using single-cell polymerase chain reaction in a patient with concomitant mantle cell lymphoma and multiple myeloma. *International Journal of Hematology* 2001;**73**:383–5.
7. Cachia AR, Diss TC, Isaacson PG. Composite mantle-cell lymphoma and plasmacytoma. *Human Pathology* 1997;**28**(11)1291–5.
8. Wang HY, Karandikar N, Payne D, Maleki A, Schultz BA, Collins R. A 3-way collision tumor of the upper respiratory tract: a composite of 2 immunophenotypically distinct mantle cell lymphoma and plasmacytoma. *Human Pathology* 2008;**39**(5):781–7.
9. Visco C, Hoeller S, Malik J, Xu-Monette ZY, Wiggins ML, Liu J, et al. Molecular characteristics of mantle cell lymphoma presenting with clonal plasma cell component. *American Journal of Surgical Pathology* 2011;**35**(2):177–89.
10. Fiancette R, Amin R, Truffinet V, Vincent-Fabert C, Cogne N, Cogne M, et al. A myeloma translocation-like model associating CCND1 with the immunoglobulin heavy-chain locus 3 enhancers does not promote by itself B-cell malignancies. *Leukemia Research* 2010;**34**:1043–51.
11. Marsaud V, Tchakarska G, Andrieux G, Liu JM, Dembele D, Jost B, et al. Cyclin K and cyclin D1b are oncogenic in myeloma cells. *Molecular Cancer* 2010;**9**:103h ttp://dx.doi.org/10.1186/1476-4598-9-103.
12. Gladden AB, Woolery R, Aggarwal P. Expression of constitutively nucleae cyclin D1 in murine lymphocytes induces B-cell lymphoma. *Oncogene* 2006;**25**(7):998–1007.
13. Tchakaska G, Roussel M, Troussard X, Bola B. Cyclin D1 inhibits mitochondrial activity in B cells. *Cancer Research* 2011;**71**:1690–9.
14. Bergsagel PL, Kuehl WM. Chromosome translocations in multiple myeloma. *Oncogene* 2001;**20**:5611–22.
15. Ronchetti D, Finelli P, Richelda R, Baldini L, Rocchini M, Viggiano L, et al. Molecular analysis of 11q13 breakpoints in multiple myeloma. *Blood* 1999;**93**(4):1330–7.